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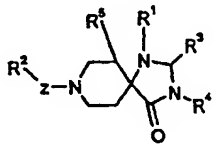
(54) Title: NOVEL TRIAZASPIRODECANONES WITH HIGH AFFINITY FOR OPIOID RECEPTOR SUBTYPES



(I)

(57) Abstract: The present invention relates to a compound of general formula (I) wherein R^1, R^2, R^3, R^4 and R^5 and z is defined in the description, or a pharmaceutically acceptable salt thereof for the treatment of migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence and/or vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes.

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TITLE

Novel triazaspirodecanones with high affinity for opioid receptor subtypes

FIELD OF INVENTION

The present invention relates to compounds of the general formula I for the treatment of migraine, non-insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence and/or vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes. The present invention also embraces pharmaceutical compositions comprising these compounds and methods of using the compounds and their pharmaceutical compositions.

BACKGROUND OF THE INVENTION

A "hot flush" is a sudden transient sensation ranging from warmth to intense heat and typically accompanied by flushing and perspiration. It is the classic sign of the menopause and the predominant complaint of menopausal women.

A positive correlation between plasma levels of calcitonin gene-related peptide (CGRP) and frequency of hot flushes in women has recently been reported (Chen et al., 1993, Lancet (342) 49), in accordance with the potent vasodilatory effect of CGRP (Brain et al., 1985, Nature, (313) 54-56).

Also, a positive correlation between CGRP antagonists and diabetes, septic shock and inflammation has been described (Feurstein, G, Willette, R and Aiyar, N., 1995, Can. J. Physiol. Pharmacol. 73: 1070-1074).

Recently, a novel heptadecapeptide, nociceptin, was discovered (Meunier et al., 1995, Nature (377) 532-535, Reinscheid et al., 1995, Science (270) 792-794).

Nociceptin and analogues thereof have been disclosed in WO 97/07212, EP 813065 and in WO 97/07208. These peptides and inhibitors thereof are said to be useful for antagonising physiologic effects of an opioid in an animal, and for treating/preventing a disease related to: hyperalgesia, neuroendocrine secretion, stress, locomotor activity, anxiety etc.

Jenck, F et. al. also found, that Orphanin FQ acts as an anxiolytic to attenuate behavioral responses to stress (PNAS Vol. 94, 1997).

It is well known that triaza-spiro compounds are vasodilating agents and morphine-like analgesics as disclosed in US 3,238,216 and US 3,155,670 by Janssen.

1,3,8-triazaspirodecanones which are nociceptin agonists have been disclosed by Hoffmann La Roche in EP 0856514 and EP 0921125.

Wichmann et al., 1999, Bioorganic and Chemistry Letters, 9:2343-2348 also describe 1,3,8-triazaspirodecanones with nociceptin activity.

SUMMARY OF THE INVENTION

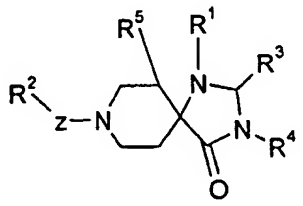
It has been found that members of a novel group of triaza-spiro compounds have high affinity for nociceptin receptors which make them useful as regulators of peripheral vasomotor effects known as hot flushes.

The present invention provides compounds of the general formula I as disclosed below or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment of Type II diabetes, septic shock, inflammation, incontinence and vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes.

Further objects will become apparent from the following description.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to compounds of the general formula I



(I)

wherein

R^1 is phenyl, aralkyl or thienyl any of which may be optionally substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy or NR^6R^7 wherein R^6 and R^7 independently are hydrogen or C_{1-6}-alkyl; or

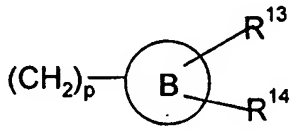
R^1 is C_{1-6}-alkyl;

R^2 is aminophenyl, C_{1-6}-monoalkylaminophenyl, C_{1-6}-dialkylaminophenyl, cyanophenyl, or C_{2-6}-alkylphenyl; or

R^2 is naphthyl, tetrahydronaphthyl, anthryl, furanyl, indanyl, indolyl, isoindolyl, benzothienyl, benzofuranyl, or dihydrobenzofuranyl; any of which may be optionally substituted with one or more halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy or trifluoromethyl;

R^3 is hydrogen, C_{1-6}-alkyl, phenyl, benzyl or acetyl;

R^4 is $(CH_2)_m$-A-N(R^9)-$(CH_2)_n R^8$ wherein
m is 1 to 8,
n is 0 to 8,
A is CH_2 or C=O,
R^8 is a group $NR^{11}R^{12}$, wherein R^{11} and R^{12} independently are hydrogen or aminoalkyl; or
R^8 is a group of the general formula (II),



(II)

wherein
B is phenyl, C_{4-8}-cycloalkyl, a saturated heterocycle or an unsaturated heterocycle;
R^{13} is hydrogen, amino, aminoalkyl, guanyl or guanylalkyl;
R^{14} is amino, aminoalkyl, guanyl or guanylalkyl;
p is 0 to 4;

R^9 is hydrogen, C_{1-4}-alkyl or aralkyl;

R^5 is hydrogen or C_{1-4}-alkyl;

z is CHR^{10} wherein R^{10} is hydrogen, C_{1-6}-alkyl, phenyl or aralkyl; or
z is C_{2-8}-alkylene, C_{2-8}-alkenylene or C_{2-8}-alkynylene; or
a pharmaceutically acceptable salt thereof.

In another embodiment the invention relates to the compound of the formula (I) wherein
R^1 is phenyl, C_{1-6}-alkyl, arylalkyl or thienyl;

R^2 is naphthyl, tetrahydronaphthyl, indanyl, benzothienyl, benzofuranyl, or dihydrobenzofuranyl any of which may be optionally substituted with one or more halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy or trifluoromethyl;

R^3 is hydrogen;

R^4 and R^5 are as described above;

z is CHR^{10} wherein R^{10} is hydrogen; or

a pharmaceutically acceptable salt thereof.

In yet another embodiment of the invention R^1 is phenyl.

In yet another embodiment of the invention R^2 is naphthyl.

In yet another embodiment of the invention R^3 is hydrogen.

In yet another embodiment of the invention R^4 is $(CH_2)_m$-A-N(R^9)-$(CH_2)_n R^8$ wherein

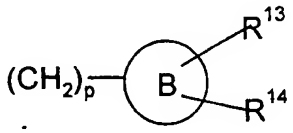
m is 1 to 4,

n is 0 to 5,

A is CH_2 or C=O,

R^8 is a group $NR^{11}R^{12}$, wherein R^{11} and R^{12} independently are aminoalkyl; or

R^8 is a group of formula (II),



(II)

wherein

B is phenyl or C_{5-7}-cycloalkyl;

R^{13} is hydrogen, amino or aminoalkyl;

R^{14} is amino or aminoalkyl;

p is 0 to 4;

R^3, R^5 and R^9 are hydrogen;

z is CH_2;

or a pharmaceutically acceptable salt thereof.

In yet another embodiment of the invention the compounds are selected from the following:

cis/trans-N-(3-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide;

trans(+)-N-(2-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide;

cis/trans- N-(4-Aminomethyl-cyclohexylmethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)acetamide;

trans-N-(4-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8triaza-spiro[4.5]dec-3-yl)acetamide; and

3-(2-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-ethyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one; or

a pharmaceutically acceptable salt thereof.

In yet another embodiment of the invention the compounds are selected from the following:

3-(3-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-propyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(2-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-ethyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(3-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-propyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(4-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-butyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(4-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-butyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one;

N-{2-[Bis-(2-amino-ethyl)-amino]-ethyl}-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide; and

N-{3-[Bis-(3-amino-propyl)-amino]-propyl}-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide; or

a pharmaceutically acceptable salt thereof.

In yet another embodiment of the invention the compounds are selected from the following:

cis/trans-N-(3-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide, di-trifluoroacetate;

trans(+)-N-(2-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide, di-trifluoroacetate;

cis/trans- N-(4-Aminomethyl-cyclohexylmethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)acetamide, di-trifluoroacetate;

trans-N-(4-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8triaza-spiro[4.5]dec-3-yl)acetamide, di-trifluoroacetate; and

3-(2-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-ethyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate).

In yet another embodiment of the invention the compounds are selected from the following:

3-(3-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-propyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate);

3-(2-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-ethyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate);

3-(3-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-propyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate);

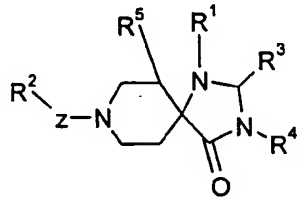
3-(4-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-butyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate);

3-(4-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-butyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetrahydrochloride;

N-{2-[Bis-(2-amino-ethyl)-amino]-ethyl}-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide, tetrahydrochloride; and

N-{3-[Bis-(3-amino-propyl)-amino]-propyl}-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide, tri-(trifluoroacetate).

As used herein the term "triaza-spirodecanone" represents a compound of formula



with various substituents as defined above.

As used herein the term "high affinity" represents an IC_{50} below 1μM.

As used herein the term "arylalkyl" refers to a straight or branched saturated carbon chain containing from 1 to 6 carbons substituted with an aromatic hydrocarbon; such as benzyl, phenethyl, 3-phenylpropyl, 1-naphtylmethyl, 2-(1-naphtyl)ethyl and the like.

As used herein the term "C_{1-6}-alkyl" represent a branched or straight alkyl group or cycloalkyl with five or six carbon in the ring. Typical C_{1-6}-alkyl groups include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, iso-pentyl, hexyl, iso-hexyl and the like.

As used herein the term "C_{1-6}-alkoxy" alone or in combination is intended to include those C_{1-6}-alkyl groups of the designated length in either a linear or branched or cyclic configuration linked through an ether oxygen having its free valence bond from the ether oxygen. Examples of linear alkoxy groups are methoxy, ethoxy, propoxy, butoxy, pentoxy and hexoxy. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy and isohexoxy. Example of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

As used herein the term "halogen" means fluorine, chlorine, bromine or iodine.

As used herein the term "amino acid residue or peptidyl residues" is also meant to comprise naturally occurring or synthetically produced amino acids linked to the compound by an amide bond.

As used herein the terms "C_{2-8}-alkylene" represent a branched or straight alkyl group having from one to the specified number of carbon atoms. Typical C_{2-8}-alkylene groups include, but are not limited to, ethylene, n-propylene, iso-propylene, butylene, iso-butylene, sec-butylene, tert-butylene, pentylene, iso-pentylene, hexylene, iso-hexylene and the like.

As used herein the terms "C_{2-8}-alkenylene" represents an olefinically unsaturated branched or straight group with at least one double bond. Examples of such groups include, but are not limited to, vinyl, 1-propenylene, allylene, iso-propenylene, 1,3-butadienylene, 1-butenylene, hexenylene, pentenylene, and the like.

As used herein the term "C_{2-8}-alkynylene" represent an unsaturated branched or straight group having at least one triple bond. Examples of such groups include, but

are not limited to, 1-propynylene, 1-butynylene, 2-butynylene, 1-pentynylene, 2-pentynylene and the like.

As used herein the term "aminoalkyl" means aminomethyl, aminoethyl, aminopropyl etc.

As used herein the term "guanylalkyl" means guanylmethyl, guanylethyl, guanylpropyl etc.

As used herein the term "saturated heterocycle" means tetrahydropyranyl, piperidyl, piperazinyl etc.

As used herein the term "unsaturated heterocycle" means pyridyl, thienyl, furanyl etc.

As used herein the term "aralkyl" means e.g. benzyl, phenylethyl, phenylpropyl.

As used herein the term "m" means an integer comprising 1, 2, 3, 4, 5, 6, 7 and 8.

As used herein the term "n" means an integer comprising 0, 1, 2, 3, 4, 5, 6, 7 and 8.

As used herein the term "p" means an integer comprising 0, 1, 2, 3 and 4.

As used herein the term "ligand" is also meant to comprise a compound with agonistic, partial agonistic or antagonistic activity specifically binding to receptor proteins.

Certain of the above defined terms may occur more than once in the above formula I, and upon such occurence each term shall be defined independently of the other.

The compounds of the present invention may have one or more asymmetric centres and it is intended that stereoisomers (optical isomers), as separated, pure or partially purified stereoisomers or racemic mixtures thereof are included in the scope of the invention.

Within the present invention, the compounds of the general formula I may be prepared in the form of pharmaceutically acceptable salts such as base or acid addition salts, especially acid-addition salts, including salts of organic acids and mineral acids. Examples of

such salts include salts of organic acids such as formic acid, fumaric acid, acetic acid, propionic acid, glycolic acid, lactic acid, pyruvic acid, oxalic acid, succinic acid, malic acid, maleic acid, tartaric acid, citric acid, benzoic acid, salicylic acid and the like. Suitable inorganic acid-addition salts include salts of hydrochloric, hydrobromic, sulphuric and phosphoric acids and the like. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2 (1977) which are known to the skilled artisan.

Also intended as pharmaceutically acceptable acid addition salts are the hydrates, which the present compounds of the general formula I are able to form.

The acid addition salts may be obtained as the direct products of compound synthesis. In the alternative, the free base may be dissolved in a suitable solvent containing the appropriate acid, and the salt isolated by evaporating the solvent or otherwise separating the salt and solvent.

The compounds of the general formula I of this invention may form solvates with standard low molecular weight solvents using methods known to a person skilled in the art.

The compounds of the general formula I may be administered in pharmaceutically acceptable acid addition salt form. Such salt forms are believed to exhibit approximately the same order of activity as the free base forms.

In yet another embodiment of the invention the compounds of the general formula I are used for the treatment of migraine, non insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence and/or vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes.

In still another embodiment of the invention the composition is in a form suitable for oral, nasal, transdermal, pulmonal, or parenteral administration.

In a further embodiment of the present invention the compounds of the general formula I is administered as a dose in the range from about 0.01 to about 5000 mg per patient per day, preferably from about 1 to about 1000 mg per patient per day, especially from about 10 to about 100 mg per patient per day, e.g. about 100 mg per patient per day.

In another aspect, the invention relates to a method for the treatment or prevention of migraine, Type II diabetes, sepsis, inflammation, incontinence and/or vasomotor disturbances, in particular the peripheral vasomotor effects known as hot flushes or hot flashes, the method comprising administering to a patient in need thereof an effective amount of compounds of the general formula I or a pharmaceutically acceptable salt thereof.

In yet another aspect, the present invention includes within its scope pharmaceutical compositions comprising, as an active ingredient, at least one of the compounds of the general formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

In yet another aspect, the invention relates to a pharmaceutical composition comprising triaza-spiro compounds with high affinity to the nociceptin receptor, or a pharmaceutically acceptable salt thereof.

In yet another aspect, the invention relates to a method of treatment symptoms of drug withdrawal, in particular abstinence symptoms occurring during withdrawal from abusive drugs.

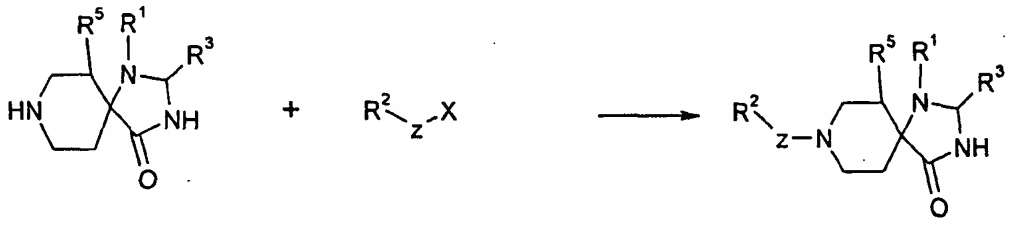
The effective, such as the therapeutically effective amount of a compounds of the general formula I will depend upon the mode of administration, on the therapy desired, form in which administered, the subject to be treated and the body weight of the subject to be treated, and the preference and experience of the physician or veterinarian in charge.

As used herein the term "treatment" is also meant to comprise prophylactic treatment.

As used herein the term "patient" comprises any mammal which may benefit from treatment or prevention of vasomotor disturbances, such as a human, especially if the mammal is a female, such as a woman. However, "patient" is not intended to be limited to a woman.

The preparation of compounds of formula I may include, but are not limited to the following methods:

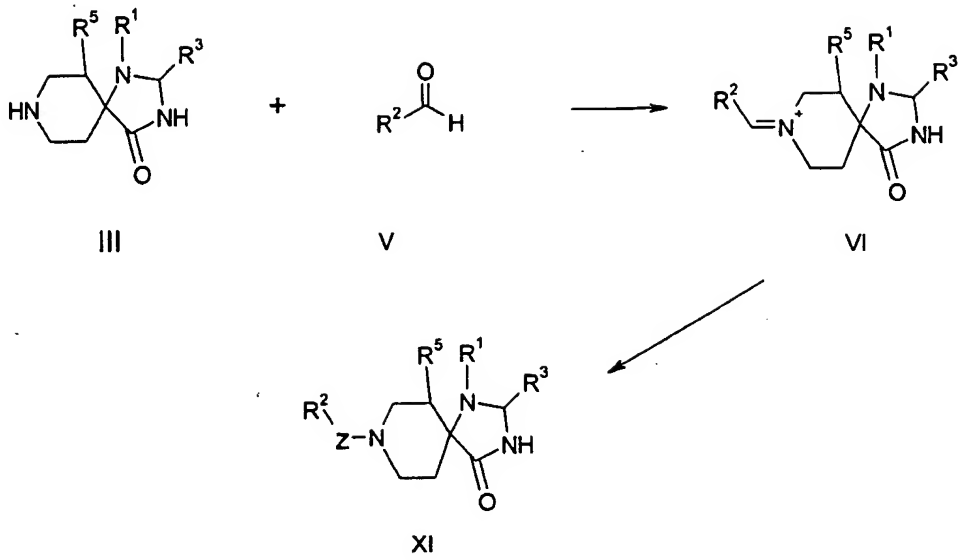
A:



III IV XI

A compound of formula (III), wherein R^1, R^3 and R^5 are as defined above may be allowed to react with a compound of formula (IV), wherein R^2 and z are defined as above and X is a suitable leaving group such as halogen, p-toluene sulphonate or mesylate, to form a compound of formula (XI) wherein R^1, R^2, R^3, R^5 and z are as defined above above. This alkylation reaction may be carried out in a solvent such as acetone, dibutylether, 2-butanone, methyl ethyl ketone, ethyl acetate, tetrahydrofuran (THF) or toluene in the presence of a base e.g. potassium carbonate and a catalyst, e.g. an alkali metal iodide at a temperature up to reflux temperature for the solvent used for e.g. 1 to 120 h. Compounds of formula (III) may be prepared by known methods, e.g. as described in US-Patent 3,238,216. Compounds of formula (IV) are commercially available or may readily be prepared by methods familiar to those skilled in the art. The compound of formula (XI) may be reacted further as described in method C or D to produce the compound of formula (I).

B:

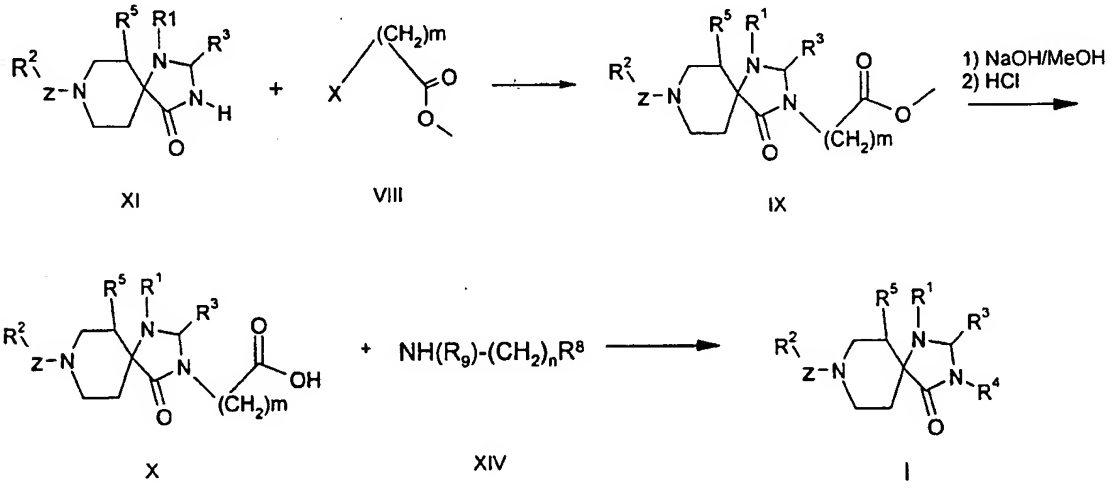


III V VI

XI

A compound of formula (III), wherein R^1, R^3 and R^5 are as defined above may be allowed to react with an aldehyde of formula (V), wherein R^2 is as defined above, to form an iminium compound of formula (VI), wherein R^1, R^2, R^3 and R^5 are as defined above. The reaction may be carried out in a suitable solvent like a lower aliphatic alcohol as e.g. ethanol or an ether as e.g. tetrahydrofuran or a mixture of these. In a second step, the formed iminium derivative of formula (VI) is then reduced to an amine of formula (XI), wherein R^1, R^2, R^3, R^5 and z are as defined above, by the addition of a suitable reducing agent, e.g. a hydride as sodium cyanoborohydride or sodium borohydride in e.g. 1 to 120 h at 20° C to reflux temperature. The compound of formula (XI) may be reacted further as described in method C or D to produce the compound of formula (I).

C:

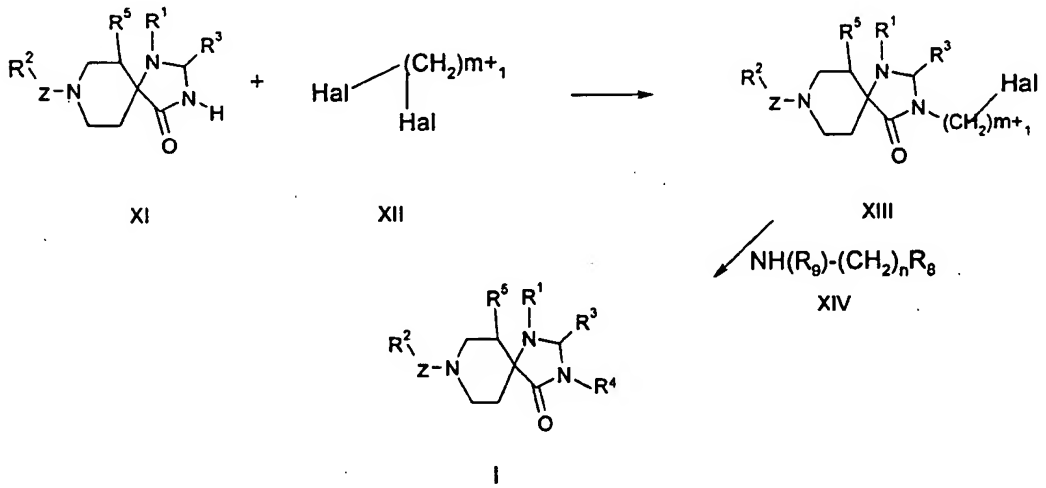


XI VIII IX

X XIV I

The compound of formula (XI), wherein R^1, R^2, R^3, R^5 and z are as defined above, may be deprotonated at N3 with a suitable base, as sodium hydride, n-butyl lithium or potassium tert.-butoxide in an aprotic solvent as e.g. dimethyl formamide or dimethylsulfoxide and subsequently allowed to react with a reagent of formula (VIII), wherein m and X are as defined above. The reaction may be carried out at temperatures from 0 °C to reflux temperature, preferably at room temperature in 1 to 24 hours, to form an ester of formula (IX), wherein R^1, R^2, R^3, R^5, z and m are as defined above. The ester of formula (IX) may be hydrolyzed to a free acid of formula (X), wherein R^1, R^2, R^3, R^5, z and m are as defined above. This acid of formula (X) may be reacted with an amine of formula (XIV), wherein R^8, R^9 and n are as defined above, to form the compound of formula (I). The coupling reaction may be carried out in a suitable solvent as e.g. dimethyl formamide or N-methylpyrrolidone using e.g. a coupling reagent from the class of the carbodiimides, a benzotriazol and an optional base. These amide couplings are well documented in the literature and commonly known. Alternatively, the acid of formula (X) may be transformed into the acid chloride with a reagent as thionyl chloride or oxalyl chloride, and the formed acid chloride may be reacted with the amine of formula (XIV) in a suitable solvent as e.g. toluene, to form the compound of formula (I).

D:



The compound of formula (XI), wherein R^1, R^2, R^3, R^5 and z are as described above, may be allowed to react with an excess of a compound of formula (XII), wherein m is as de-

fined above and Hal is a halogen group or halogen substitute groups such as p-toluene-sulphonate, or mesylate) on different carbon atoms. The reaction may be allowed to take place in the presence of a base such as sodium hydride in a solvent such as dimethyl-formamide or dimethylsulfoxide at temperatures between room temperature up to reflux, to produce an intermediate compound of formula (XIII), wherein R^1, R^2, R^3, R^5, m and Hal are as defined above. The compound of formula (XIII) is allowed to react further with a compound of formula (XIV), wherein R^8, R^9 and n are as defined above, and which contains a primary or secondary amino group, which displaces the halogen atom or halogen substitute group. This reaction may be performed in the presence of a base such as potassium carbonate in a solvent such as acetonitrile or dimethylformamide at temperatures between room temperature and reflux.

A pharmaceutical composition for use in accordance with the present invention comprises, one or more compound of the formula I as active ingredient(s), or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions containing compounds of the formula I of the present invention may be prepared by conventional techniques, e.g. as described in Remington: The Science and Practise of Pharmacy, 19th Ed., 1995. The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

Typical compositions include compounds of the general formula I or a pharmaceutically acceptable acid addition salt thereof, associated with a pharmaceutically acceptable excipient which may be a carrier or a diluent or be diluted by a carrier, or enclosed within a carrier which can be in the form of a capsule, sachet, paper or other container. In making the compositions, conventional techniques for the preparation of pharmaceutical compositions may be used. For example, the active compound will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier which may be in the form of a ampoule, capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active compound. The active compound can be adsorbed on a granular solid container for example in a sachet. Some examples of suitable carriers are water, salt

solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatine, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents. The formulations of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The pharmaceutical compositions can be sterilized and mixed, if desired, with auxiliary agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or colouring substances and the like, which do not deleteriously react with the active compounds.

The route of administration may be any route, which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral e.g. rectal, depot, subcutaneous, intravenous, intraurethral, intramuscular, intranasal, ophthalmic solution or an ointment.

If a solid carrier is used for oral administration, the preparation may be tabletted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

For nasal administration, the preparation may contain compounds of the general formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhydroxylated castor oil.

Tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like are particularly suitable for oral application. Preferable carriers for tablets, dragees, or capsules include lactose, corn starch, and/or potato starch. A syrup or elixir can be used in cases where a sweetened vehicle can be employed.

A typical tablet which may be prepared by conventional tabletting techniques may contain:

Core:	
Active compound (as free compound or salt thereof)	100 mg
Colloidal silicon dioxide (Aerosil)	1.5 mg
Cellulose, microcryst. (Avicel)	70 mg
Modified cellulose gum (Ac-Di-Sol)	7.5 mg
Magnesium stearate	Ad.
Coating:	
HPMC approx.	9 mg
*Mywacett 9-40 T approx.	0.9 mg

*Acylated monoglyceride used as plasticizer for film coating.

Any novel feature or combination of features described herein is considered essential to this invention.

PHARMACOLOGICAL EFFECTS:

Male Sprague Dawley rats (300±25 g) were anaesthetized with pentobarbital sodium (50 mg/kg i.p.) and polyethylene catheters were positioned in both femoral veins for the intravenous administration of drugs, such as nociceptin and analogues, and into the left femoral artery in order to measure arterial blood pressure and heart rate. The trachea was cannulated with polyethylene tubing and the rat was pithed, ventilated and drug

treated as described by Nuki Y. et al. (Effects of Dorsal Rhizotomy on Depressor Response to Spinal Cord Stimulation Mediated by Endogenous Calcitonin Gene-related Peptide in the Pithed Rat. J. Neurosurg. 1993; 79:899-904).

EXAMPLES

The process for preparing compounds of formula I and preparations containing them is further illustrated in the following examples, which, however, are not to be construed as limiting.

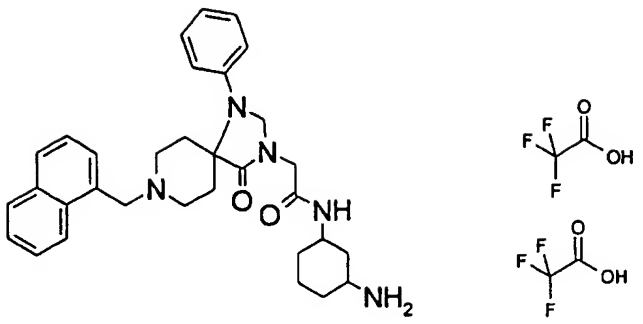
Hereinafter, TLC is thin layer chromatography, $CDCl_3$ is deuterio chloroform and DMSO-d_6 is hexadeuterio dimethylsulfoxide. The structures of the compounds are confirmed by either elemental analysis or NMR, where peaks assigned to characteristic protons in the title compounds are presented where appropriate. ^1H NMR shifts (δ_H) are given in parts per million (ppm).

HPLC-MS analyses were performed on a PE Sciex API 100 LC/MS System using a YMC ODS-A 120 Å s - 5µ 3 mm x 50 mm column and positive ionspray with a flow rate of 20 µL/minute. The column was eluted with a linear gradient of 5-90% A, 85-0% B and 10% C in 7.5 minutes at a flow rate of 1.5 ml/min.(solvent A = acetonitrile, solvent B = water and solvent C = 0.5% trifluoroacetic acid in water).

M.p. is melting point and is given in °C and is not corrected. Column chromatography was carried out using the technique described by W.C. Still et al, J. Org. Chem. (1978), 43, 2923-2925 on Merck silica gel 60 (Art. 9385). Compounds used as starting materials are either known compounds or compounds, which can readily be prepared by methods known per se.

EXAMPLE 1

cis/trans-N-(3-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide, di-trifluoroacetate



Wang resin (3.27 g, 3.5 mmol) was placed in a solid synthesis flask equipped with a glass frit and swelled in dry tetrahydrofuran (50 ml) for 15 minutes. Solid N,N-carbonyldiimidazole (3.41 g, 2 mmol) was added and the mixture was agitated under nitrogen gas protection over night. The solution was removed by suction and the resin was washed with tetrahydrofuran (2x 50 ml) and dichloromethane (2x 50 ml). (cis/trans)-1,3-Diaminocyclohexane (1.60 g, 14 mmol) was dissolved in dichloromethane (35 ml) and added to the resin, followed by diisopropylamine (0.91 g, 7 mmol). The mixture was agitated under nitrogen gas protection over night. The solution was removed by suction, the resin was washed with dichloromethane (4x 50 ml) and diethyl ether (1x 50 ml) and dried in vacuo.

To a solution of (8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid (0.344 g, 0.8 mmol) in dry N,N-dimethylformamide (7.5 ml) was added 1-hydroxybenzotriazole (0.108 g, 0.8 mmol) and N,N'-diisopropylcarbodiimide (0.101 g, 0.8 mmol). The mixture was stirred at room temperature for 1 h and added to the above prepared amine loaded resin (0.22 g, 0.2 mmol). The mixture was agitated over night, after the first 15 minutes diisopropylamine (0.103 g, 0.8 mmol) was added. The solution was removed by suction, the resin was washed with N,N'-dimethylformamide (2x 5 ml), dichloromethane (4x 5 ml), methanol (2x 5 ml) and dichloromethane (2x 5 ml) and dried in vacuo.

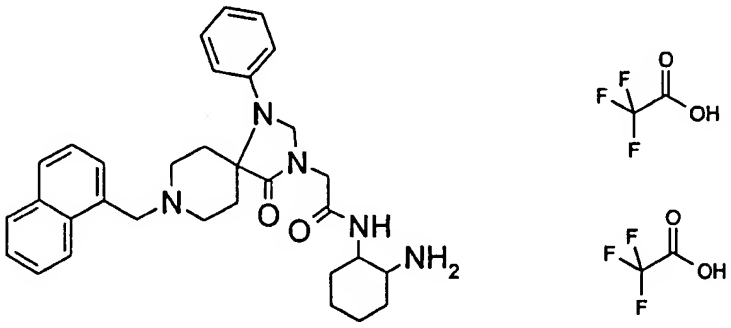
The resin was treated with dichloromethane/ trifluoroacetic acid (1:1) (5 ml) for 2 h at room temperature. The filtrate was collected, evaporated in vacuo and stripped with acetonitrile. The crude product was purified by preparative HPLC using a C18-silica column. The column was eluted with a linear gradient of 10-90% acetonitrile and 90-10% 0.1% trifluoroacetic acid in 15 minutes. The pure fraction was evaporated in vacuo, dissolved in water/acetonitrile (1:1) and freeze dried, to afford the title compound (0.015 g, 10% yield) as a powder.

LC/MS: m/e = 526.4 (MH^+); RT = 4.46 min.

The compounds of EXAMPLES 2 to 4 were synthesized using the above described method and employing the appropriate diamines:

EXAMPLE 2

trans(+)-N-(2-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide, di-trifluoroacetate

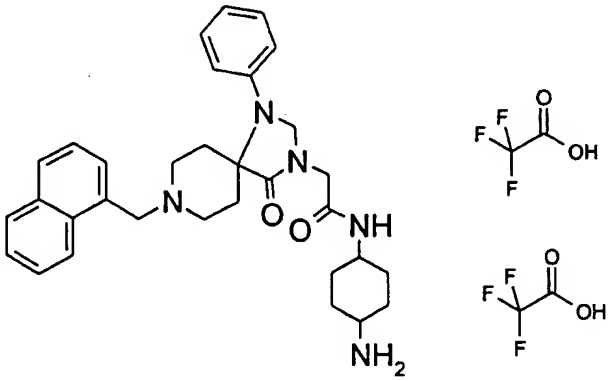


Freeze dried powder (0.014 g, 9% yield)

LC/MS: m/e = 526.4 (MH^+); RT = 4.26 min.

EXAMPLE 3

cis/trans- N-(4-Aminomethyl-cyclohexylmethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)acetamide, di-trifluoroacetate

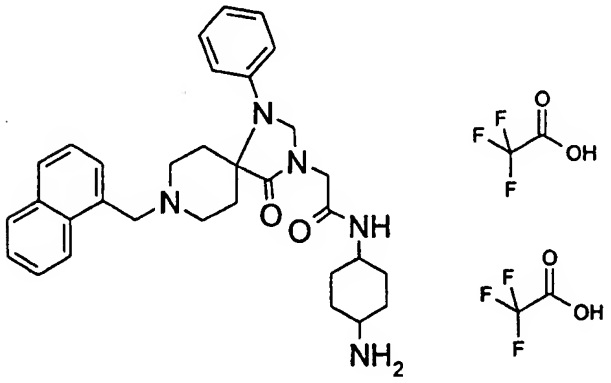


Freeze dried powder (0.022 g, 14% yield)

LC/MS: m/e = 554.4 (MH^+); RT = 4.32 min.

EXAMPLE 4

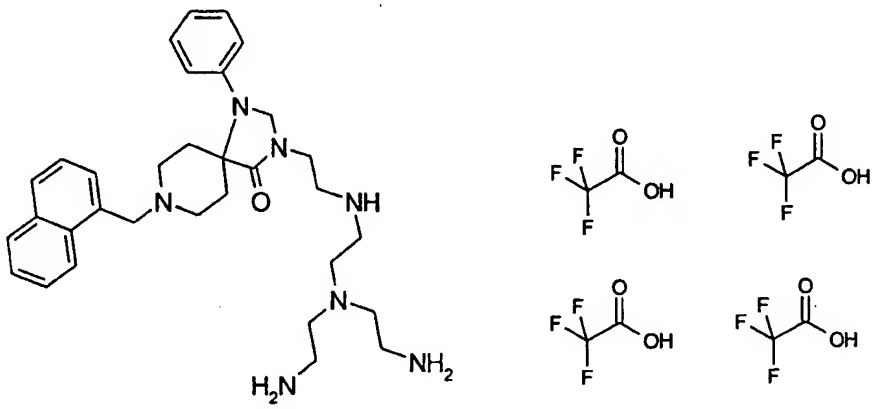
trans-N-(4-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8triaza-spiro[4.5]dec-3-yl)acetamide, di-trifluoroacetate



Freeze dried powder (0.023 g, 15% yield)
LC/MS: m/e = 526.4 (MH^+); RT = 4.46 min.

EXAMPLE 5

3-(2-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-ethyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate)



Sodium hydride, 60% (0.624 g, 15.6 mmol) was suspended in dry heptane (5 ml) and stirred under nitrogen for 5 minutes. The solvent was decanted and dry N,N'-dimethyl formamide (6 ml) was added. 8-Naphthalen-1-ylmethyl-1-phenyl-1,3,8-triazaspiro [4.5]decan-4-one (4.46 g, 12 mmol), dissolved in dry dimethyl formamide (42 ml) was added dropwise under cooling in an ice bath. The mixture was stirred at 0 °C for 1 h. The resulting solution of deprotonated 1-phenyl-8-naphthalen-1-ylmethyl-1,3,8-triazaspiro

[4.5]decan-4-one was added dropwise to a stirred solution of 1,2-dibromoethane (11.3 g, 60 mmol) in dimethyl formamide (10 ml) at room temperature and stirring was continued over night. The mixture was then diluted with water (100 ml) and extracted with toluene (2x 50 ml). The combined organic phases were successively washed with water (2x 25 ml) and brine (25 ml), dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash chromatography on silica with toluene/ethyl acatate/triethylamine (80:20:2) as the eluent. The pure fractions were concentrated in vacuo, dissolved in tetrahydrofuran (20 ml) and the hydrochloride was precipitated by the dropwise addition of a solution of hydrogen chloride in ether in excess. The precipitate was washed with a 1:1 mixture of tetrahydrofuran and ether and dried, affording 3-(2-bromoethyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one (1.87 g, 30% yield) as a powder.

LC/MS: m/e = 480.4 (MH^+); RT = 5.40 min.

The above bromide (0.386 g, 0.75 mmol), together with tris-(2-aminoethyl)amine (0.61 g, 3.75 mmol), potassium carbonate (0.415 g, 3 mmol) and sodium iodide (0.112 g, 0.75 mmol) was heated to reflux in 2-butanone (7.5 ml) for 16 h. The solution was cooled, filtered and concentrated in vacuo. The residue was purified by preparative HPLC using a C18-silica column. The column was eluted with a linear gradient of 10-90% acetonitrile and 90-10% 0.1% trifluoroacetic acid in 15 minutes. The pure fraction was evaporated in vacuo, dissolved in water(5 ml) and acetonitrile (1 ml) and freeze dried, affording the title compound (0.272 g, 35% yield) as a powder.

LC/MS): m/e = 544.4 (MH^+); RT = 4.18 min.

Calculated for $C_{32}H_{45}N_7O$, 4 CF_3COOH, 2.25 H_2O:

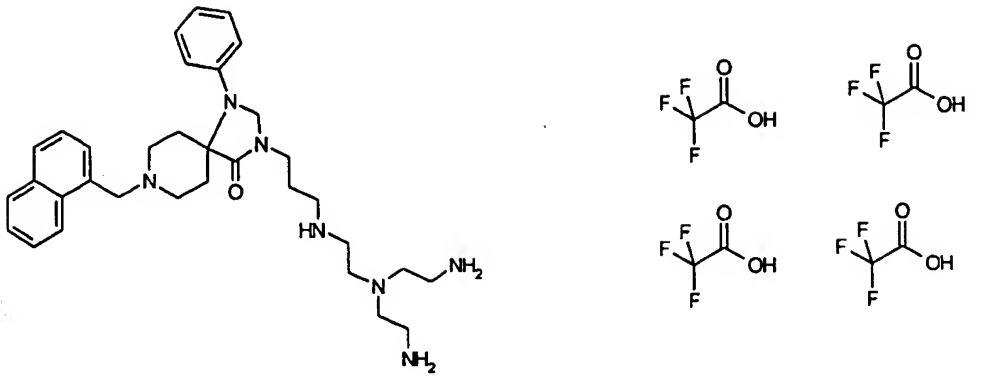
C, 46.18%; H, 5.18%; N, 9.42%; Found :

C, 46.03%; H, 5.04%; N, 9.24%.

The compounds of EXAMPLES 6 to 10 were synthesized using the methods described in EXAMPLE 5 and employing the appropriate α, ω–dibromoalkanes and amines:

EXAMPLE 6

3-(3-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-propyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate)

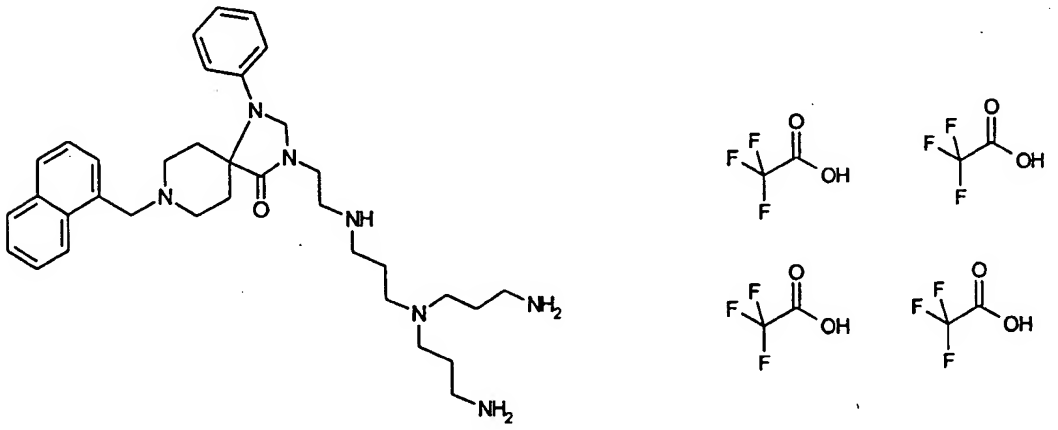


Freeze dried powder (0.044 g, 14% yield)

LC/MS): m/e = 558.4 (MH^+); RT = 3.62 min.

EXAMPLE 7

3-(2-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-ethyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate)

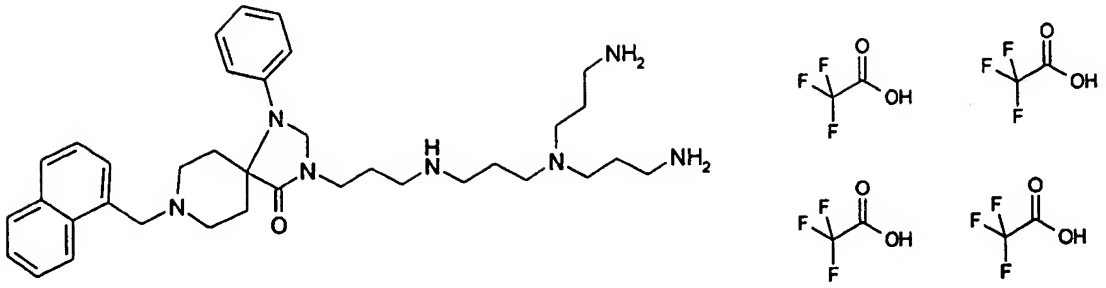


Freeze dried powder (0.034 g, 11% yield)

LC/MS): m/e = 586.4 (MH^+); RT = 3.87 min.

EXAMPLE 8

3-(3-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-propyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate)

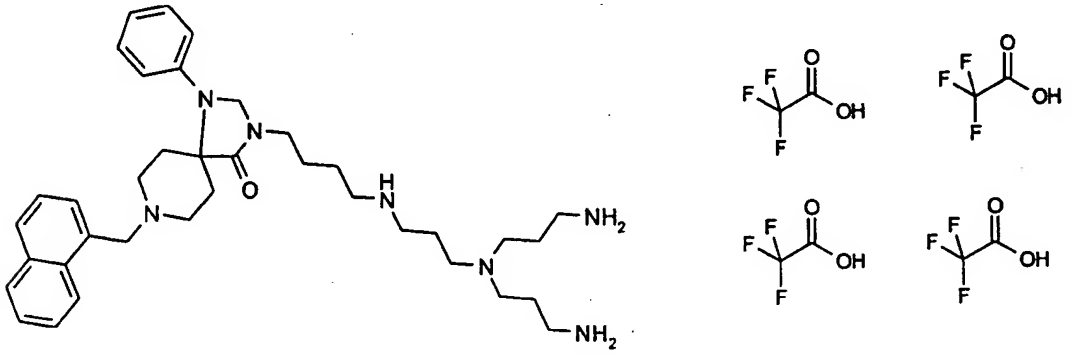


Freeze dried powder (0.089 g, 34% yield)

LC/MS): m/e = 600.4 (MH^+); RT = 3.68 min.

EXAMPLE 9

3-(4-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-butyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate)

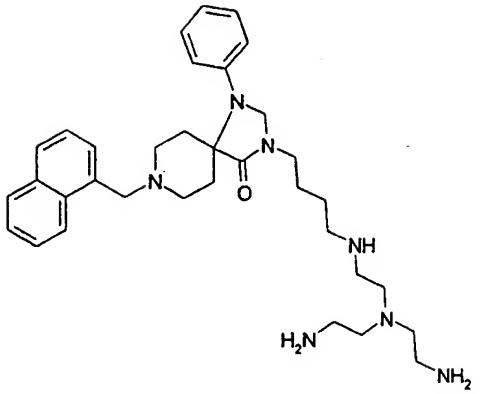


Freeze dried powder (0.084 g, 32% yield)

LC/MS): m/e = 614.4 (MH^+); RT = 3.82 min.

EXAMPLE 10

3-(4-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-butyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetrahydrochloride



The freeze dried tetrafluoroacetate of the title compound (0.145 g) was dissolved in 1N hydrochloric acid (2.5 ml) and the solution was concentrated in vacuo. This procedure was repeated with 1N hydrochloric acid (2.5 ml) and with water (2.5 ml). The hydrochloride was dissolved in boiling ethanol (4 ml), the solution cooled to room temperature and ether was added (15 ml). The precipitate was filtered and dried, affording the title compound (0.128 g) as a powder.

LC/MS): m/e = 572.4 (MH^+); RT = 3.98 min.

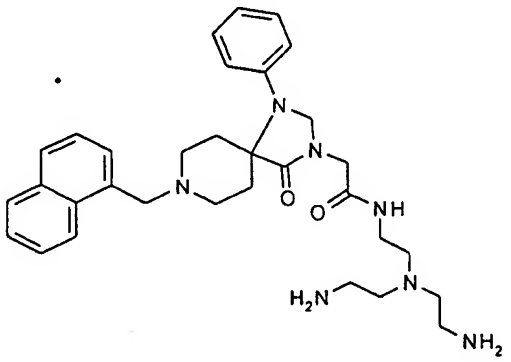
Calculated for $C_{34}H_{49}N_7O$, 4 HCl, 2.5 H_2O:

C, 53.54%; H, 7.66%; N, 12.93%; Found :

C, 53.55%; H, 7.59%; N, 12.75%.

EXAMPLE 11

N-{2-[Bis-(2-amino-ethyl)-amino]-ethyl}-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide, tetrahydrochloride



Solid (8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetic acid (21.0 g, 45 mmol) was added in portions to neat oxalyl chloride (200 ml) under stirring. The mixture was heated to reflux for 30 min. After cooling to room temperature, dry toluene (500 ml) was added. The resulting precipitate was filtered, washed with toluene and dried, affording (8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetyl chloride, hydrochloride (18.7 g, 86% yield) as a powder.

LC/MS): m/e = 444.2 (MH^+); RT = 4.85 min.

The above acid chloride (16.8 g, 34.7 mmol) was added to a stirred solution of tris-(2-aminoethyl)amine (35.5 g, 243 mmol) in dry toluene (35 ml), cooled in an ice bath. The resulting suspension was stirred at 5 °C for 1h and at room temperature for 2 h. Toluene (180 ml) was added and the mixture was filtered. The filtrate was evaporated in vacuo, the resulting oil was dissolved in acetonitrile (400 ml) and the solution was neutralized with trifluoroacetic acid (90 ml) under cooling in an ice bath. Precipitated salts were removed by filtration and the filtrate was evaporated in vacuo. The crude product was purified by preparative HPLC using a C18-silica column. The column was eluted with a linear gradient of 5-95% acetonitrile and 95-5% 0.1% trifluoroacetic acid in 20 minutes. The pure fractions were evaporated in vacuo, stripped twice with 1N hydrochloric acid (150 ml) and once with water (150 ml). The resulting powder was dissolved in ethanol (100 ml) and ether was added (100 ml). The precipitate was filtered off and dried, affording the title compound (4.64 g, 18%) as a powder.

LC/MS): m/e = 558.4 (MH^+); RT = 3.83 min.

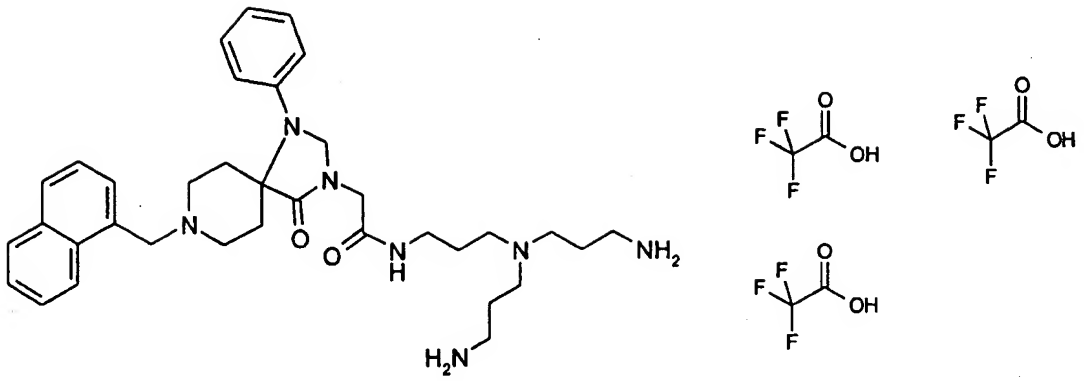
Calculated for $C_{32}H_{43}N_7O_2$, 4 HCl, 3.25 H_2O:

C, 50.43%; H, 7.08%; N, 12.94%; Found :

C, 50.13%; H, 7.08%; N, 13.12%.

EXAMPLE 12

N-{3-[Bis-(3-amino-propyl)-amino]-propyl}-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide, tri-(trifluoroacetate)

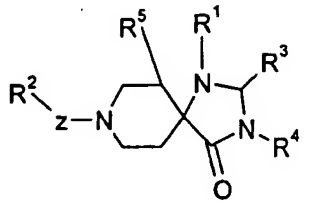


Following the same procedure as described in EXAMPLE 11 and using tris-(3-amino-propyl)amine as the amine, the title compound (47 mg, 17% yield) was obtained as a freeze dried powder.

LC/MS): m/e = 600.4 (MH^+); RT = 3.73 min.

CLAIMS

1. A compound of the general formula I



(I)

wherein

R^1 is phenyl, aralkyl or thienyl, optionally substituted with one or more of halogen, cyano, nitro, trifluoromethyl, C_{1-6}-alkyl, hydroxy, C_{1-6}-alkoxy or NR^6R^7 wherein R^6 and R^7 independently are hydrogen or C_{1-6}-alkyl, or

R^1 is C_{1-6}-alkyl;

R^2 is aminophenyl, C_{1-6}-monoalkylaminophenyl, C_{1-6}-dialkylaminophenyl, cyanophenyl, C_{2-6}-alkylphenyl; or

R^2 is naphthyl, tetrahydronaphthyl, anthryl, furanyl, indanyl, indolyl, isoindolyl, benzothienyl, benzofuranyl or dihydrobenzofuranyl any of which may be substituted with one or more halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy or trifluoromethyl;

R^3 is hydrogen, C_{1-6}-alkyl, phenyl, benzyl or acetyl;

R^4 is $(CH_2)_m$-A-N(R^9)-$(CH_2)_nR^8$, wherein

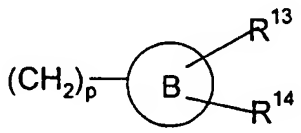
m is 1 to 8,

n is 0 to 8,

A is CH_2 or C=O,

R^8 is a group $NR^{11}R^{12}$, wherein R^{11} and R^{12} independently are hydrogen or aminoalkyl; or

R^8 is a group of the general formula (II),



(II)

wherein

B is phenyl, C_{4-8}-cycloalkyl, a saturated heterocycle or an unsaturated heterocycle;

R^{13} is hydrogen, amino, aminoalkyl, guanyl or guanylalkyl;

R^{14} is amino, aminoalkyl, guanyl or guanylalkyl;

p is 0 to 4;

R^9 is hydrogen, C_{1-4}-alkyl or aralkyl;

R^5 is hydrogen or C_{1-4}-alkyl;

z is CHR^{10} wherein R^{10} is hydrogen, C_{1-6}-alkyl, phenyl or aralkyl - or z is C_{2-8}-alkylene, C_{2-8}-alkenylene or C_{2-8}-alkynylene; or

a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein

R^1 is C_{1-6}-alkyl, phenyl, arylalkyl or thienyl;

R^2 is naphthyl, tetrahydronaphthyl, indanyl, benzothienyl, benzofuranyl, or dihydrobenzofuranyl any of which may be substituted with one or more of halogen, C_{1-6}-alkyl, C_{1-6}-alkoxy or trifluoromethyl;

R^3 is hydrogen;

R^4 is $(CH_2)_m$-A-N(R^9)-$(CH_2)_n R^8$, wherein

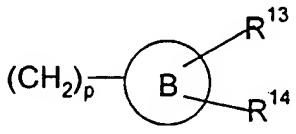
m is 1 to 8,

n is 0 to 8,

A is CH_2 or C=O,

R^8 is a group $NR^{11}R^{12}$, wherein R^{11} and R^{12} independently are hydrogen or aminoalkyl, or

R^8 is a group of structure (II),



(II)

wherein

B is phenyl, C_{4-8}-cycloalkyl, a saturated heterocycle or an unsaturated heterocycle;

R^{13} is hydrogen, amino, aminoalkyl, guanyl or guanylalkyl

R^{14} is amino, aminoalkyl, guanyl or guanylalkyl;

p is 0 to 4;

R^9 is hydrogen, C_{1-4}-alkyl or aralkyl;

R^5 is hydrogen or C_{1-4}-alkyl;

z is CHR^{10} wherein R^{10} is hydrogen; or

a pharmaceutically acceptable salt thereof.

3. A compound according to any of the claims 1-2 wherein

R^1 is phenyl;

R^2 is naphthyl,

R^3 is hydrogen;

R^4 is $(CH_2)_m$-A-N(R^9)-$(CH_2)_n R^8$,wherein

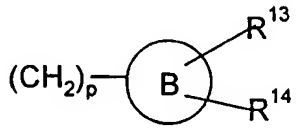
m is 1 to 8,

n is 0 to 8,

A is CH_2 or C=O,

R^8 is a group $NR^{11}R^{12}$, wherein R^{11} and R^{12} independently are hydrogen or aminoalkyl; or

R^8 is a group of formula (II),



(II)

wherein

B is phenyl, C_{4-8}-cycloalkyl, a saturated heterocycle or a unsaturated heterocycle;

R^{13} is hydrogen, amino, aminoalkyl, guanyl or guanylalkyl;

R^{14} is amino, aminoalkyl, guanyl or guanylalkyl;

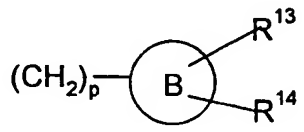
p is 0 to 4;

R^9 is hydrogen, C_{1-4}-alkyl or aralkyl;

R^5 is hydrogen;

z is CHR^{10} wherein R^{10} is hydrogen; or
a pharmaceutically acceptable salt thereof.

4. A compound according to any of the claims 1-3 wherein
R^1 is phenyl;
R^2 is naphthyl;
R^4 is $(CH_2)_m$-A-N(R^9)-$(CH_2)_n R^8$, wherein
m is 1 to 4,
n is 0 to 5,
A is $-CH_2$ or -C=O,
R^8 is a group $NR^{11}R^{12}$, wherein R^{11} and R^{12} are aminoalkyl; or
R^8 is a group of formula (II),



(II)

wherein
B is phenyl or C_{5-7}-cycloalkyl;
R^{13} is hydrogen, amino or aminoalkyl;
R^{14} is amino or aminoalkyl;
p is 0 to 4;

R^3, R^5 and R^9 are hydrogen;

z is CHR^{10} wherein R^{10} is hydrogen; or
a pharmaceutically acceptable salt thereof.

5. A compound according to any of the claims 1-4 selected from the following:

cis/trans-N-(3-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide;

trans(+)-N-(2-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide;

cis/trans- N-(4-Aminomethyl-cyclohexylmethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)acetamide;

trans-N-(4-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8triaza-spiro[4.5]dec-3-yl)acetamide;

3-(2-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-ethyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one; or

a pharmaceutically acceptable salt thereof.

6. A compound according to any of the claims 1-4 selected from the following:

3-(3-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-propyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(2-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-ethyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(3-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-propyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(4-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-butyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one;

3-(4-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-butyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one;

N-{2-[Bis-(2-amino-ethyl)-amino]-ethyl}-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide; and

N-{3-[Bis-(3-amino-propyl)-amino]-propyl}-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide; or

a pharmaceutically acceptable salt thereof.

7. A compound according to any of the claims 1-5 selected from the following:

cis/trans-N-(3-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide, di-trifluoroacetate;

trans(+)-N-(2-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide, di-trifluoroacetate;

cis/trans- N-(4-Aminomethyl-cyclohexylmethyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)acetamide, di-trifluoroacetate;

trans-N-(4-Amino-cyclohexyl)-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8triaza-spiro[4.5]dec-3-yl)acetamide, di-trifluoroacetate; and

3-(2-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-ethyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate).

8. A compound according to any of the claims 1-4 and 6 selected from the following:

3-(3-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-propyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate);

3-(2-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-ethyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate);

3-(3-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-propyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate);

3-(4-{3-[Bis-(3-amino-propyl)-amino]-propylamino}-butyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetra-(trifluoroacetate);

3-(4-{2-[Bis-(2-amino-ethyl)-amino]-ethylamino}-butyl)-8-naphthalen-1-ylmethyl-1-phenyl-1,3,8-triaza-spiro[4.5]decan-4-one, tetrahydrochloride;

N-{2-[Bis-(2-amino-ethyl)-amino]-ethyl}-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide, tetrahydrochloride; and

N-{3-[Bis-(3-amino-propyl)-amino]-propyl}-2-(8-naphthalen-1-ylmethyl-4-oxo-1-phenyl-1,3,8-triaza-spiro[4.5]dec-3-yl)-acetamide, tri-(trifluoroacetate).

9. A pharmaceutical composition comprising a compound according to any of the claims 1-8 together with a pharmaceutical acceptable acid addition salt thereof and a pharmaceutically acceptable carrier or diluent.

10. A pharmaceutical composition suitable for use in the treatment of migraine, non-insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence and/or vasomotor disturbances comprising an amount of compound I according to any of the claims 1-8 together with a pharmaceutical carrier or diluent.

11. A pharmaceutical composition according to any of the claims 9 or 10 wherein it is in a form of an oral dosage unit or a form suitable for oral, nasal, transdermal, pulmonal parenteral dosage unit containing 0.1 to about 1000 mg per patient per day.

12. Use of a compound according to any of the claims 1-8 for preparation of a medicament.

13. Use of a compound according to any of the claims 1-8 for the preparation of a medicament for treatment of migraine, non-insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence and/or vasomotor disturbances.

14. Use of a compound according to any of the claims 1-8 for the preparation of a

medicament for treatment, prevention, elimination, alleviation and/or amelioration of disturbances or symptoms related to the nociceptin system.

15. Use of a compound according to any of the claims 1-8 for the preparation of a medicament for treatment of vasomotor disturbances, especially hot flushes.

16. A pharmaceutical composition suitable for use in the treatment of migraine, non-insulin dependent diabetes mellitus (type II diabetes), sepsis, inflammation, incontinence and/or vasomotor disturbances comprising an amount of compound I according to any of the claims 1-8 together with a pharmaceutical carrier or diluent.

17. A method of treating hot flushes in a subject in need of such treatment comprising the step of administering to said object an amount of a compound according to any of the claims 1-8 which is effective for the alleviation of such ailment.

18. A method of treating hot flushes in a subject in need of such treatment comprising the step of administering to said object an amount of a compound according to any of the claims 1-8 which is effective for the alleviation of such ailment in the form of a pharmaceutical composition thereof, in which it is present together with a pharmaceutically acceptable carrier or diluent.

19. Any novel feature or combination of features described herein.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 00/00641

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D471/10 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 99 59997 A (NOVONORDISK AS) 25 November 1999 (1999-11-25) the whole document ---	1-5,7, 9-16
P,X	WO 00 06545 A (SCHERING CORP) 10 February 2000 (2000-02-10) the whole document ---	1-4,9-16
A	US 3 238 216 A (JANSSEN P A J) 1 March 1966 (1966-03-01) the whole document ---	1-16
A	US 3 155 670 A (JANSSEN P A J) 3 November 1964 (1964-11-03) the whole document ---	1-16
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 February 2001	23. 04. 2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Göran Karlsson

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 00/00641

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 856 514 A (HOFFMANN LA ROCHE) 5 August 1998 (1998-08-05) the whole document ---	1-16
A	EP 0 921 125 A (HOFFMANN LA ROCHE) 9 June 1999 (1999-06-09) the whole document -----	1-16

1

INTERNATIONAL SEARCH REPORT

International Application No
PCT/DK 00/00641

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		EP 1080091 A	07-03-2001
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		US 6043366 A	28-03-2000
		ZA 9811128 A	07-06-1999

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 00/00641

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first she t)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 17 18
because they relate to subject matter not required to be searched by this Authority, namely:

A method for treatment of the human or animal body by therapy,see rule 39.1

2. [X] Claims Nos.: 19
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 19

Claim 19 does not clearly define the matter for which protection is sought. A meaningful search has therefore not been performed,c.f. Article 6

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.